Criteria for Use of Meperidine

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

These criteria are based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. This guidance is intended to assist practitioners in providing consistent, high quality, cost effective drug therapy. These criteria are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.

INTRODUCTION

Meperidine is a phenylpiperadine opioid agonist analgesic with anticholinergic, serotonergic, and noradrenergic effects. While there is evidence suggesting that its analgesic effects are not superior to that of other opioid agonist analgesics,[1-6] meperidine is one of the most efficacious agents available for treatment of post-operative shivering.[7,8] It is also efficacious for prevention of post-operative shivering[9] and treatment[10] or prevention[11] of amphotericin B-induced rigors. Contrary to common belief, meperidine increases biliary sphincter pressure, and there is a lack of outcome-based clinical evidence demonstrating that it has an advantage over other opioids in patients with acute pancreatitis.[12]

Meperidine can cause neurotoxicity, a potentially severe adverse effect that is due to the accumulation of a metabolite, normeperidine. It is difficult to predict which individuals will experience neurotoxic effects and how severe the reaction will be.

Meperidine also has the potential to cause life-threatening serotonin syndrome when used in patients who are concurrently or were recently taking monoamine oxidase inhibitors (within 2 to 3 weeks) or other agents with serotonin reuptake inhibiting properties. Furthermore, meperidine causes negative changes in mood while other opioid agonist analgesics induce positive changes.[13] The risk of delirium is also higher with meperidine than other opioid analgesics.[14,15]

The use of meperidine requires careful patient monitoring for neuroexcitatory effects and tracking of dosage to reduce the risk of neurotoxicity, as well as extra vigilance to identify concomitant or recent use of serotonergic drugs to prevent potentially fatal drug interactions. Since other opioid agonist analgesics have similar analgesic efficacy, lower risk of neurotoxicity at usual therapeutic doses, and lower risk for serotonin syndrome due to drug interactions, the use of meperidine in the VA should be restricted to the situations outlined below.

VA CRITERIA FOR USE

Other, safer parenteral opioids should generally be used for analgesia instead of meperidine, particularly in vulnerable elders. (*Vulnerable elders* are defined as persons age 65 years and older who are at increased risk for death or functional decline over 2 years.[16,17])

Appropriate Use	Inappropriate Use/Increased Risk
Peri-procedural analgesia, as in gastrointestinal, surgical and interventional radiologic procedures.	Orally administered meperidine
Treatment or prevention of drug- or blood-product–induced rigors (off-label use).	Long-term pain management
Treatment or prevention of post-anesthesia shivering (off-label use).	
Short-term (< 24-h) parenteral administration for management of moderate to severe acute pain, including patient-controlled analgesia, in patients who – have a documented hypersensitivity to morphine or hydromorphone, or intolerance to other opioid analgesics (e.g., morphine, hydromorphone, and fentanyl); and – require a total dose of less than 600 mg in 24 h.	

FDA-APPROVED INDICATIONS

Oral and parenteral: Relief of moderate to severe pain

Parenteral: Preoperative medication, support of anesthesia, obstetrical analgesia

PRECAUTIONS / CONTRAINDICATIONS

Hypersensitivity to meperidine

Multiple doses for patients with renal dysfunction

Hepatic impairment

Monoamine oxidase inhibitors (within 2 to 3 weeks) or agents with serotonergic activity

Multiple doses for patients with seizure disorder

Coma or severe respiratory depression

DOSAGE AND ADMINISTRATION

Intravenous is preferred over intramuscular administration because of large interpatient variability in absorption of meperidine from muscle tissue.[18] When intravenous access is not available, subcutaneous injections are appropriate for occasional use but intramuscular injections are preferred for repeated doses. Orally administered meperidine is not recommended in the VA because it has variable bioavailability, may produce less analgesia, and may result in greater formation of normeperidine due to extensive first-pass metabolism. Dosage is not established for off-label use of epidural and intrathecal routes of administration.

Analgesia: 100 to 150 mg i.m./s.c. every 2 to 4 hours. For patient-controlled intravenous analgesia: 25 to 50 mg (0.5 to 1 mg/kg) load, 5 to 25 mg demand bolus, lockout 6 to 8 min. For peri-procedural analgesia, the recommended total dose should not exceed 100 mg.

The VA/DoD *Clinical Practice Guideline on the Management of Post-Operative Pain* recommends limiting the total dose of parenteral meperidine to a maximum of 600 mg in 24 hours and the duration to 24 hours.[19]

Post-operative shivering (off-label use): Meperidine 25 mg i.v. has been found to be efficacious.[7] The optimal dose is not established.

Drug- or blood product–induced shivering (off-label use): Dose is not established and well-designed trials are lacking. For treatment of shivering due to amphotericin B, when meperidine (100 mg/ml) was slowly infused i.v. until shivering stopped, the mean effective dose was 45 mg (range: 25 to 60 mg).[10] For prevention of shivering due to amphotericin B, a dose of 0.70 mg/kg i.v. was found to be efficacious.[11]

Dosing in special populations

Hepatic disease: The bioavailability and half-life of orally administered meperidine are increased in patients with cirrhosis. Although conversion of meperidine to normeperidine is decreased, accumulation of the metabolite and neurotoxicity may occur with repeated doses due to reduction in normeperidine elimination. Use of meperidine is contraindicated due to increased risk of toxicity from accumulation of meperidine and normeperidine.

Renal disease: Meperidine is contraindicated in patients with renal impairment because normeperidine can accumulate in patients with renal disease (half-life of 34 hours with renal dysfunction). Severe renal insufficiency may be considered when the creatinine clearance is $\leq$ 20 ml/minute. In patients $\leq$ 50 years old, this is equal to a serum creatinine of approximately 5 mg/dl. However, in older patients ($\geq$ 75 years old) the serum creatinine is about 2.5 mg/dl for the creatinine clearance to be approximately 20 ml/minute.

Elderly: Reduce the initial dose and cautiously titrate to achieve desired response. [16,17]

Patients taking phenothiazines or other tranquilizers: Reduce dose of meperidine by 25% to 50% since these drugs potentiate the effects of meperidine.

MONITORING

Signs and symptoms of neurotoxicity: anxiety, shaky feelings, delirium, nervousness, hyperreflexia, tremors, twitches, multifocal myoclonus, generalized seizures. Risk factors for neurotoxicity include renal dysfunction; high, frequent doses; and co-administration of agents that may induce seizures or lower the seizure threshold (such as phenothiazines).[13,20]

However, myoclonus and seizures may occur in patients with normal renal function, at relatively low doses, and after short duration of therapy (e.g., 260 to 540 mg per day over 3 to 10 days).[13,21] Meperidine-induced neurotoxicity has often occurred after two days of repeated dosing,[13,21] but toxic effects have occurred in less than 24 hours (e.g., 17 hours after a patient received a total of 750 mg i.m./i.v.[22]) Premonitory symptoms of severe neurotoxicity may be absent or subtle.[22,23] Naloxone does not reverse the neurotoxic effects of meperidine.

Cumulative dose and duration of meperidine: do not exceed 600 mg per 24 hours or duration of 24 hours.

DRUG INTERACTIONS

Table 1 Selected drug interactions with meperidine

Interacting Drug(s)	Effects	Prevention	Documentation
Monoamine oxidase inhibitors (MAOIs)[†] Selegiline (MAO-B inhibitor)	Serotonin syndrome (agitation, seizures, diaphoresis, fever, coma, apnea, death)	Avoid use of meperidine for several weeks after discontinuation of MAOIs, and avoid concomitant use. Use other opioids with caution.	Numerous case reports with various nonselective MAOIs[24] Single case report with selegiline[25]
Selective serotonin reuptake inhibitors (SSRIs)[‡]	Serotonin syndrome (agitation, confusion, hypertension, tachycardia, diaphoresis, diarrhea)	Use caution; monitor patient for adverse effects. Concomitant use of meperidine and SSRIs is not a listed contraindication.	Single case report with fluoxetine[26]
Sibutramine[‖]	Serotonin syndrome (CNS irritability, motor weakness, shivering, myoclonus, altered consciousness)	Avoid concomitant use. If concomitant use is unavoidable, carefully monitor patient for adverse effects.	Package insert precaution[27]
Barbiturate anesthetics (e.g., thiopental)	Decreased dose of thiopental required to induce anesthesia; increased risk of apnea	Decrease dose of thiopental by about 40%. Use precautions usually used in anesthesia.	Controlled study, case reports[24]
Phenothiazines	Excessive sedation and hypotension. *Positive effects:* Decreased opioid analgesic dosage and less nausea and vomiting.	Benefit-to-risk ratio does not support concomitant use.	Two controlled studies[24]
Ritonavir	Possibly decreased efficacy and increased neurotoxicity	Avoid dosage increase and long-term use of meperidine with ritonavir or avoid concomitant use.	Package insert[28] Pharmacokinetic study[29]

Source: Drug Interaction Facts online[24]

[†] *Monoamine oxidase inhibitors*: phenelzine (Nardil), tranylcypromine (Parnate), isocarboxazid (Marplan), selegiline/deprenyl (Eldepryl)

[‡] *Selective serotonin reuptake inhibitors*: citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac, Sarafem), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft)

[‖] Sibutramine (Meridia), an anorexiant with serotonin reuptake inhibiting properties

COST

Table 2 Comparative drug acquisition costs (lowest VA prices)

	Analgesia				Postoperative shivering[†]			Drug-induced shivering[†]
	Fentanyl	Hydromorphone	**Meperidine**	Morphine	Alfentanil	Doxapram	**Meperidine**	**Meperidine**
Dose (mg)[‡]	0.1	2	75	10	0.25	100	25	45
Route	i.v.	i.m.	i.m.	i.m.	i.v.	i.v.	i.v.	i.v.
Cost	$0.45	$0.50	$0.14	$0.38	$3.40	$10.88	$0.26	$0.26

Lowest VA prices as of June 2003; all drugs shown are on the VA National Formulary

[†] In a systematic review that compared antishivering agents, **clonidine 0.15 mg i.v. and doxapram 100 mg i.v. were similar in efficacy to meperidine 25 mg i.v.** for treatment of postoperative shivering. For each of these three agents, number-needed-to-treat was less than 2 for one to stop shivering within 5 minutes who would have continued to shiver had they all received a placebo.[7] **Meperidine was superior to alfentanil (NNT 2.4) and ketanserin (NNT 2.3).** There was insufficient data to compare other drugs, including nalbuphine, nefopam, and tramadol i.v.[7] A single study found that **nefopam was superior to meperidine** for prevention and treatment of amphotericin B-induced shivering.[11] Clonidine i.v. and nalbuphine are not on the VA National Formulary. Tramadol i.v., nefopam, and ketanserin are not available in the U.S.

[‡] Doses for analgesia are estimated equianalgesic doses; and drug-induced shivering dose for meperidine is the estimated mean effective dose found by Burks (1980).[10]

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